# Synthesis of a *trans*-fused perhydroindan analog of hispidospermidin[†]

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**Abstract**

A reductive alkylation–halolactonization–free radical cyclization reaction sequence plays a pivotal role in a synthesis of the hispidospermidin analog **3** from *m*-toluic acid. © 2000 Elsevier Science Ltd. All rights reserved.

Hispidospermidin (**1**) is a recently isolated tetracyclic spermidine alkaloid inhibitor of mammalian phospholipase C (PLC), an enzyme regarded as a target for drug development against proliferative diseases.[1] Whereas **1** is a micromolar inhibitor of mammalian PLC, amine **2** is virtually inactive, and both spermine and spermidine weakly inhibit mammalian PLC.[1] This suggests that the polyamine moiety in **1** is essential for PLC inhibitory activity and that the hydrophobic cage merely potentiates inhibitory action. Two total syntheses of this natural product have been reported.[2,3] This paper describes a synthesis of hispidospermidin analog **3** using a reductive alkylation–halolactonization–free radical cyclization sequence to construct the *trans*-fused perhydroindan substructure of the natural product.[4,5]



The synthesis of **3** began with preparation of bridged perhydroindan **10**, as shown in Scheme 1. Birch reduction of *m*-toluic acid (**4**), followed by in situ alkylation of the resulting dianion,

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[†] This paper is dedicated to Professor Harry Wasserman on the occasion of his 80th birthday.

provided dihydrobenzoic acid derivative **5**.[6] Treatment of **5** with iodine in aqueous tetra-hydrofuran gave iodolactone **6** in 80% overall yield from **4**. Hydrolysis of the acetal using aqueous formic acid provided aldehyde **7** (85%), which was converted into hydrazone **8** in 95% yield upon reaction with 1-amino-2-phenylaziridine[7] in methanol. Treatment of **8** with tri-*n*-butyltin hydride in benzene under reflux provided *trans*-fused perhydroindan **9** in 80% yield. Whereas the crude product contained trace amounts of a compound suspected to have a 2-phenylethyl group appended to $C_8$, it could be recrystallized to provide pure **9**.[8] This free radical cyclization relies on the excellent methodology developed by Kim[9] within the context of a route to *trans*-fused perhydroindans previously developed in our laboratories.[4] The synthesis of **10** was completed in 50% yield by a two-step sequence involving lithium aluminum hydride reduction to provide a diol, followed by formation of the primary mesylate and cyclization.
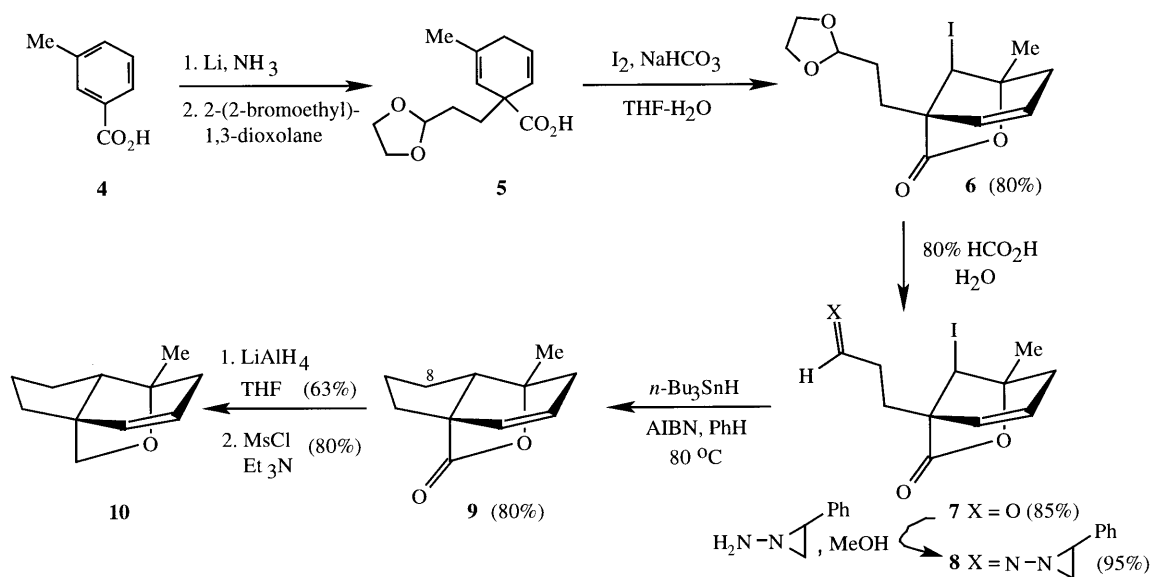


Scheme 1.

The synthesis of **3** continued as described in Scheme 2. Installation of the $C_{11}$ nitrogen functionality was accomplished using a four-step reaction sequence. Thus, epoxidation of the olefin from the least hindered face gave **11**. Rearrangement of the epoxide using lithium diethylamide provided allylic alcohol **12** in 88% yield.[10] Conversion of **12** to trichloroacetimidate **13**, followed by thermal rearrangement, gave **14** in 62% overall yield.[11] Catalytic hydrogenation of the olefin was accompanied by hydrogenolysis of one carbon–chlorine bond to give **15** in 90% yield. Hydrolysis of amide **16**, followed by acylation of the resulting amine **16** with acid **17** gave amide **18** in 60% yield.[3] Lithium aluminum hydride reduction of **18** gave the target spermidine derivative **3** in 69% yield.

From the standpoint of biological activity, hispidospermidin analog **3** has not yet been evaluated as a mammalian PLC inhibitor. It has been found, however, that the hispidospermidin analog **3**, hispidospermidin (**1**),[12] adamantane analog **19**,[13] cyclohexyl analog **20**,[13] spermidine, and spermine, show no obvious inhibition of bacterial phosphotidylinositol-specific PLC at concentrations up to 10 mM.[14] From the standpoint of a possible synthesis of the natural product **1**, this route incorporates potentially useful functionality for completion of the cage structure, but does not provide for incorporation of the $C_6$ methyl group in its current form.[15]
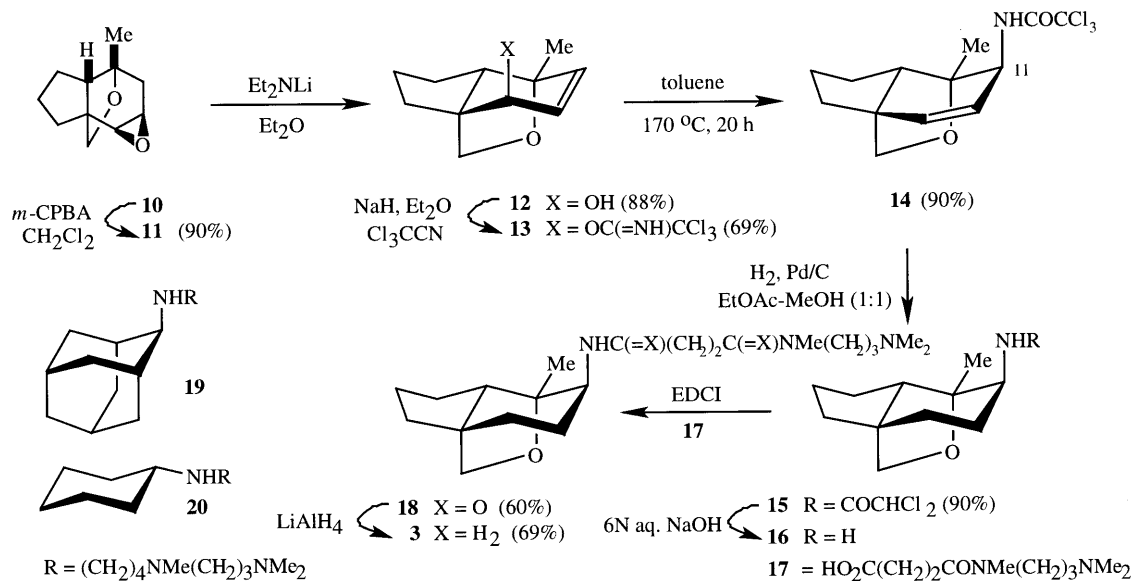
Scheme 2.

## Acknowledgements

## References

1. Yanagisawa, M.; Sakai, A.; Adachi, K.; Sano, T.; Watanabe, K.; Tanaka, Y.; Okuda, T. *J. Antibiot.* **1994**, *47*, 6. Ohtsuka, T.; Itezono, Y.; Nakayama, N.; Sakai, A.; Shimma, N.; Yokose, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 1.
2. (a) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 6686. (b) Frontier, A. J.; Raghavan, S.; Danishefsky, S. *J. Am. Chem. Soc.* **2000**, *122*, 6151.
3. Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039.
4. Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782. Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210.
5. This research is abstracted in part from the PhD thesis of David A. Ellis, The Ohio State University, 1999.
6. Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnenpathius, G.; De Mos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.
7. Muller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 114.
8. This product presumably comes from addition of a $C_8$ radical to styrene generated in the ring-forming cyclization–fragmentation process. Please note that the hispidospermidin numbering system is used throughout this paper.
9. Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882.
10. Crandall, J. K.; Lin, L.-H. C. *J. Org. Chem.* **1968**, *33*, 2375.
11. Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.
12. We thank Dr. Masahiro Aoki of the Nippon Roche Research Center for kindly supplying a sample of hispidospermidin.

13. Compounds **19** and **20** were prepared from adamantylamine and cyclohexylamine in 45 and 46% yields, respectively, using the same protocol used to convert amine **16** into the hispidospermidin analog **3**. The synthesis and some biological properties of **19** were reported by others during the preparation of this manuscript.[2b]

14. We thank Professor Ming-Daw Tsai and his students (L.Z.) for performing these assays in the Department of Chemistry at The Ohio State University.

15. Melting points of solids obtained during the course of this research follow: **6** (78.5–81°C), **7** (88–90°C), **8** (117°C/dec), **9** (54.5–56.3°C), **13** (73.5–75.5°C), **14** (155.3–159.9°C), **15** (134.2–136.5°C).